PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent appln. of :	Heng Wang, et al.
Appln. No:	10/566,697
Filed:	May 10, 2006
For:	**METHOD OF PREPARING EPITOPES CHIMERIC GENE VACCINE**
Confirm No.	9761
Examiner:	Teresa D. Wessendorf
Art Unit:	1639
Docket No:	282-08

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Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This appeal brief is being submitted electronically on September 21, 2009 in support of the Notice of Appeal filed on July 15, 2009.

A petition for a one-month extension of time accompanies this brief. This appeal brief is being timely filed within the extended period.

I. Real Party in Interest

The real party in interest is the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, a Chinese non-profit institution.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of the Claims

Claims 2-4, 8-10, and 13-25 have been finally rejected.

Claims 1, 5-7 and 11-12 have been cancelled.

The claims on appeal are claims 2-4, 8-10, and 13-25.

IV. Status of Amendment

There were no amendments filed subsequent to final rejection.

V. Summary of the Claimed Subject Matter

As embodied in independent claim 23, the present invention provides a method for preparing polyepitope chimeric gene vaccines (specification, page 4, lines 26-27). This method includes several steps. The first step is selecting, synthesizing and cloning into a vector a plurality of nucleic acid molecules each encoding a single epitope of an antigen of interest (page 4, line 31-page 5, line 2). The second step is to construct nucleic acid molecules encoding randomly combined bi-epitopes in the vectors of the first step by isocaudamer linkage (page 5, lines 3-4). This step is followed by the step of randomly assembling the nucleic acid molecules encoding by-epitopes of the second step into polyepitope chimeric genes with different lengths (page 5, lines 5-7). Next, the polyepitope chimeric genes are isolated into a plurality of different length ranges and cloned into expression vectors to obtain polyepitope chimeric gene expression libraries (page 5, lines 8-10). These expression libraries correspond to the different length ranges into which the polyepitope chimeric genes were isolated (page 5, lines 10-11). In the next step, the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries is assessed (page 5, lines 13-14), and at least one polyepitope chimeric gene library based on diversity is selected for use in preparing polyepitope chimeric gene vaccines (page 5, lines 18-20).

As embodied in independent claim 13, the present invention provides a method for preparing polyepitope chimeric gene vaccines (specification, page 4, lines 26-27). This method includes several steps. The first step is selecting, synthesizing and cloning into a vector a plurality of nucleic acid molecules each encoding a single epitope of an

antigen of interest (page 4, line 31-page 5, line 2). The second step is to construct nucleic acid molecules encoding randomly combined bi-epitopes in the vectors of the first step by isocaudamer linkage (page 5, lines 3-4). This step is followed by the step of randomly assembling the nucleic acid molecules encoding by-epitopes of the second step into polyepitope chimeric genes with different lengths (page 5, lines 5-7). Next, the polyepitope chimeric genes are isolated into a plurality of different length ranges and cloned into expression vectors to obtain polyepitope chimeric gene expression libraries (page 5, lines 8-10). These expression libraries correspond to the different length ranges into which the polyepitope chimeric genes were isolated (page 5, lines 10-11). In the next step, the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries is assessed (page 5, lines 13-14). The next step includes immunizing animals with the polyepitope chimeric gene expression libraries to provide expression products of the genes, and detecting the immunogenicity of the expression products of the genes (page 5, lines 15-18). This method also includes selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope gene expression libraries and the immunogenicity of the expression products of the genes in the polyepitope gene expression libraries (page 5, lines 18-20). Finally, the method includes the step of screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines (page 5, lines 21-23).

VI. Grounds of Rejection to be Reviewed on Appeal

A. Claims 2-4, 8-10 and 13-25 stand finally rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in that the disclosure does not support the claim breadth.

B. Claims 2-4, 8-10 and 13-25 stand finally rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, in that the specification does not provide support for alleged new matter in the amended claims.

C. Claims 2-4, 8-10 and 13-25 stand finally rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention.

D. Claims 2-3, 8-9 and 13-25 stand finally rejected under 35 U.S.C. 102(e) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over Chengtao, Lin et al., Chinese J. of Biochemistry (Zhongguo Shenwu Huaxui Fe Fenzi Shengwu Xuebao) (1999), 12(b), 974-977 ("Lin").

E. Claims 2-3, 8-9 and 13-25 stand finally rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,0264,443 ("Sette et al.") or U.S. Patent 6,602,510 ("Fikes") in view of U.S. Patent 6,291,214 (Richards et al.) or applicants' admission of known prior art.

VII. Argument

A. Claims 2-4, 8-10 and 13-25 Have Adequate Written Description and the Rejection Under 35 U.S.C. 112, First Paragraph, Should Be Reversed

1. Argument with respect to Claims 2-4, 8-10 and 13-25

The Examiner has committed legal error by finally rejecting claims 2-4, 8-10 and 13-25 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, on the ground that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner's first error lies in her failure to provide any factual basis for her legal conclusion. The Examiner had an obligation to do so in order to ground a *prima*

facie case of lack of adequate written description. "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992). She has not met her burden here.

The Examiner states that the specification fails to provide an adequate written description of the claimed method utilizing gene vaccine components of such scope particularly a library of random gene sequences. In particular, the Examiner notes that the specification describes a method of making a polyepitopic chimeric gene vaccine obtained from the single organism, *Plasmodium falciparum*, and that other than this single embodied organism, no other organism has been shown to produce polyepitopic chimeric gene vaccines. Further, the Examiner states that the disclosure does not indicate that the single embodied organism can be applied to any type of organism, nor does the disclosure disclose which nor how the different epitopes in the numerous epitopes of an organism can be derived to produce the polyepitopic chimeric gene vaccines. The Examiner objects that "[t]he disclosure does not indicate that the single embodied organism can be applied to any type of organism" (sic) (Office Action of 7/8/09, page 3, lines 10-11).

Underlying the Examiner's argument is the assumption that the subject method employing epitopes is somehow dependent on the nature of the organism. The Examiner fails to provide any factual basis for this assumption, which on its face contradicts common sense. Underlying the spectacular success of modern biological science is the assumption of the unity of life, expressed, for example, in the many common enzymatic functions shared across diverse species, reflected in common amino acid sequences, and thus necessarily common epitopes.

The Examiner asserts that in vaccine formation there is the issue of where the combination of more epitopes creates many possibilities thus, making it impractical to

assemble or construct library as used as a vaccine. However, the present invention provides a method of assembling such libraries. The Examiner provides no evidence that the present method is impractical, and vague speculation is not substitute for a factual ground for a rejection.

The Examiner further states that it is impractical to assemble and construct polyepitopic gene vaccines let alone a library because it is complicated, costly and requires much work. Again, this is speculation upon which the Examiner bases her rejection. The Examiner fails to provide any factual basis for her speculation.

The Examiner also states that more importantly, an answer as to how to effectively design polyepitope genes and overcome the variability of pathogens is required for the development of gene vaccines. The Examiner cites as an example, Li M. et al., Chin. Med. J. Engl., 112 (8), 691-7, particularly the paragraph bridging pages 691—670. However, this is one of the problems addressed by the present invention.

The Examiner correctly observes that the life cycle of *Plasmodium falciparum* which causes malignant malaria severely affecting human health is complicated and comprises four stages comprising asexual reproduction and sexual reproduction in humans and sexual reproduction and sporogony in mosquitoes. The Examiner reviews the exoerythrocytic (liver) and erythrocytic stages in humans as well as the gametocyte and sporozoite stages in mosquitoes, and further observes that such complex biological traits cause *Plasmodium falciparum* to have highly variable response against the immunoprotection of the host and drugs.

The Examiner asserts that it is not apparent how the different length ranges for the numerous different organisms can be ascertained based only on the single species, *Plasmodia falciparum,* given that the same organism in different species such as, for example, humans are different. The Examiner fails to provide any explanation as to what she means by "length ranges" although the context suggests she means lengths of

nucleic acids or genes or epitopes. The rejection is thus not intelligible and should be reversed for this reason.

The Examiner further states that it is well-known in the art that under representation or overrepresentation of these different size ranges may not produce the epitope essential for vaccine formation. The Examiner failed to provide any evidentiary support for this statement, and applicants question the accuracy of this statement.

The presently claimed invention is drawn to a method for preparing polyepitope chimeric gene vaccines, not to such a gene vaccine itself. The products of the method are claimed in presently withdrawn claims 5, 6, 11 and 12. The Examiner identifies the difficulties in engineering an effective polyepitope gene vaccine. However, it is just such difficulties that the presently claimed method is intended to overcome, and its success in doing so is indicia of its patentability.

As the Examiner acknowledges, it is particularly difficult to construct a library of polyepitope chimeric gene vaccines in the case of a difficult organism such as *Plasmodia falciparum* which grows through four separate life stages.

Applicants' success in doing so, as evidenced by the examples in the applicants' disclosure, shows the strength of the presently claimed method. Applicants' method is of general application, and is not in any way restricted to epitopes of antigens produced by any specific organism, such as *Plasmodia falciparum*.

The method is of broad application, and the epitopes employed to prepare polyepitope chimeric gene vaccines can be obtained from antigens related to other infectious diseases, as well as tumor or autoimmune diseases (claim 8).

Applicants' exemplification of their method using a particularly difficult organism is an unmistakable indication that they were in possession of the invention claimed at the time the present application was filed.

The Examiner does not controvert that success has been achieved in solving the problems she has identified for malaria's *P. falciparum*. Thus, this rejection should have been withdrawn with respect to dependent claims 4 and 10 drawn to the method of the present invention drawn to this species.

Nevertheless, the Examiner contends that the disclosure has not correlated the single species to the numerous polyepitopic present in any organism or *P. falciparum* of different strains.

This is the Examiner's second error in making her rejection: She has confused biological "species" with the patent law concept of "species."

The Examiner states that there is no guidance or direction given in the specification that would lead one skilled in the art to the different epitopes in different antigens in any organism or antigens in any kind of tumors.

However, applicants have not claimed a method for identifying epitopes. The Examiner does not assert that epitopes are unknown for other antigens for other organisms or for antigens for tumors. Indeed, applicants respectfully submit that such epitopes are well known in the art, and consequently, there is no need to pad the disclosure with extensive lists of what is already known in the art.

The Examiner further states that it is not readily apparent from the general statements in the specification or applicants' arguments as to the experimental conditions being applicable for one as applicable for all. However, applicants do not claims any specific "experimental conditions." The Examiner seems to be arguing that the specification is not enabling. However, such consideration are simply not logically relevant to her written description rejection.

This Examiner opines that the art is too complex because of the numerous unforeseen factors/effects even for a single individual gene, let alone a library (i.e., collection of millions of genes). The Examiner provides no factual support for her

assertion that other genes from other organisms are too complex for application of the presently claimed process.

The Examiner in her final rejection expressly draws applicants' attention to the newly submitted Cai reference (Vaccine). The Examiner states that Cai shows at e.g., page 275, that the slightest change in one parameter, e.g., temperature, affect the method, even as applied to an already specific polypepitopic peptide as *P. falciparum*.

However, the Examiner has misread the reference, a factual error. The reference states at page 274 that "[w]ith the isocaudamer technique, no mutation can happen during the epitope shuffling procedure, and it is much preferred over PCR amplification that can easily be contaminated by external DNA." The authors go on to note that they had initially tried to "undertake PCR amplification of all open reading frames in the shuffling procedure" and to ligate the PCR products into DNA vaccine vectors, but satisfactory results were not obtained. The authors go on to speculate that this approach failed because differences in the melting temperature "for each of the epitope DNA fragments may have caused fusion failure." Thus, they are referring to an alternative, unsuccessful technique, and not the presently claimed method as apparently misstated by the Examiner. The authors nevertheless propose a solution to the apparently problem: selecting a specific melting temperature for the PCR process based on the sequence-dependent melting temperatures of the epitope sequences. Id. at 276.

The Examiner asks rhetorically how much more for an enormous polyepitope contained in any or all kinds of antigenic epitope(s)? Again, the Examiner relies upon her own speculation rather than facts to make her rejection. It should be reversed for this reason.

The Examiner deems that the applicants, at the time of filing, have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the

invention of any species other than the one disclosed, citing In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir.2004).

However, the Examiner has provided no such evidence, but merely her own speculation. There is no evidence of record tending to show that the presently claimed method could not be applied to epitopes from other organisms, and the common sense suggests the exact opposite conclusion.

The Examiner states that one may not preempt an unduly large field by the expedient of making broad prophetic statements in the specification and claim unless the accuracy of such statements is sufficiently supported by well-established chemical principles or by sufficient number of examples. However, the techniques employed in the method of the present invention employ the well documented, long established chemical principles in cloning genes, PCR amplification, et al. The Examiner has provided no factual basis to believe the same techniques and method would not be applicable to epitopes from other organisms.

The Examiner cites "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed (genus) subject matter sufficient to distinguish it from other materials," citing University of California v. Eli Lilly, 43 USPQ 2d 1398, 1405 (1997), quoting Fiefs v. Revel, 25 USPQ2d 1601, 16106 (Fed. Cir. 1993. However, applicants are not claiming a chemical species or genus.

Applicants respectfully contend that the Examiner has not carried her burden of showing that subject matter of the presently amended claims is not adequately described. In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996). The rejection entered under 35 U.S.C. 112, first paragraph, for lack of written description, should be withdrawn for this reason.

2. Argument With Respect to Claims 4 and10

The Examiner has conceded her rejection is not applicable to those claims which are expressly limited to *Plasmodium falciparum*. Applicants thus separately argue that this rejection should be reversed with respect to claims 4 and 10.

3. Argument With Respect to Claims 2-4, 8-10 and 13-25 There Is No Written Description Requirement

Applicants respectfully request that the Board reverse this rejection on the ground that case law does not support the Examiner's view that a separate written description requirement as to method claims, and that Judge Lin's view of 35 U.S.C. 112, first paragraph, is correct. Univ. of Rochester v. G.D. Searle & Co., Inc., 375 F.3d 1303, 1325-27 (Fed. Cir. 2004) (Linn, J., dissenting from denial of rehearing en banc); Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 987-89 (Fed. Cir. 2002) (Linn, J., dissenting from denial of rehearing en banc). Section 112, paragraph 1 requires no more of the specification than a disclosure that is sufficient to enable a person having ordinary skill in the art to make and use the invention. As noted above, the Examiner is actually relying on non-enablement argument to support her lack of written description requirement. The rejection should be reversed for this reason.

B. The Rejection of Claims 2-4, 8-10 and 13-25 Under 35 U.S.C. 112, First Paragraph for Including New Matter Should Be Reversed

1. Argument With Respect to Claims 2-4. 8-10, 13-14, 16-18, and 23-25.

The Examiner states that new claims 15 and 19-22 which recite "predetermined antigen epitope" and "specific immunological type" and "measured by a single strand conformation polymorphism" are not supported by the specification as filed, and thus constitute new matter. However, none of claims 2-4, 8-10, 13-14, 16-18 or 23-25 contain any of the language to which the Examiner has objected, yet the Examiner has rejected these claims as well. There is no logical basis for the rejection of these claims

on that basis, and the rejection should accordingly be reversed as to those claims for that reason.

2. Argument With Respect to Claims 15 and 19-22.

The Examiner has entered this rejection because she could not find exactly the same terms in the specification. This is legal error grounded upon factual error.

While the specific language of the claims may not be disclosed *ipsis verbis* in the specification, *ipsis verbis* support is not required. Fujikawa v. Wattanasin, 93 F.3d 1559, 1570 (Fed. Cir. 1996). In this case literal support exists in the specification as filed for all challenged terms, other than "predetermined" which otherwise fully supported.

Support for the challenged language can be found in the specification as follows:

"predetermined antigen epitope":

The tem expressly "antigen epitope of interest" appears in the Detailed Description of the Invention section of the specification as filed, in the paragraph bridging pages 10 and 11. In this context, "of interest" provides support for "predetermined." Specific antigen epitopes are "predetermined" by being "of interest."

"specific immunological type":

The tem expressly appears in the Detailed Description of the Invention section of the specification as filed, in the paragraph bridging pages 10 and 11.

"measured by single strand conformation polymorphism":

This term expressly appears in Example 3, on page 18, lines 11-12 of the specification as filed, and Example 3 details such measurement as a step of the presently claimed process.

There is no new matter in amended claims 15 and 19-22, which are fully supported by the application as filed.

This rejection should be reversed.

C. The Rejection of Claims 2-4, 8-10 and 13-25 Under 35 U.S.C. 112, Second Paragraph, Should Be Reversed

1. Argument With Respect to Claims 2-4, 8-10 14-18 and 23-25

The Examiner objects to the use of the term "predetermined" in claims 19-22, the term "type" in claim 20, and two expressions in claim 13, as rendering the respective claims indefinite. However, none of claims 2-4, 8-10, 14-18 or 23-25 contain any of the terms or expression to which the Examiner has objected, yet the Examiner has rejected these claims as well. There is no logical basis for the rejection of these claims on that basis, and the rejection should accordingly be reversed as to those claims for that reason.

2. Argument With Respect to Claims 13 and 19-22

The Examiner states that claim 13 recites the limitation in step e) "the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries" and step f) (ii) "the immunogenicity of the expression products." The Examiner concludes that there is insufficient antecedent basis for these limitations in the claim. This is factual error. Step (d)(iii) of claim 13 expressly refers to "polyepitope chimeric gene expression libraries." Further step (f)(i) expressly refers to "expression products." The rejection should be reversed.

The Examiner states that the term "predetermined" in claims 19-22 is a relative term which renders the claim indefinite. The Examiner states that the term "predetermined" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner further states that it is unclear as to basis or standard by which the antigen epitope has been or can be predetermined, especially in the absence of positive support in the as-filed disclosure.

This is factual error. The Examiner has failed to provide any factual support for her assertion that "predetermined" would not be reasonably apprised by the scope of the invention by the use of this term which has long been used in U.S. patent practice.[1]

The Examiner states that regarding claim 20, the phrase "type" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "type"), thereby rendering the scope of the claim(s) unascertainable, especially in the absence of positive support in the specification.

This is factual error. The Examiner has failed to provide any factual support for her assertion that "type" would not be reasonably apprised by the scope of the invention by the use of this term which has long been used in U.S. patent practice an in fact appears in most patents.[2]

The rejection should be reversed.

D. The Rejection of Claims 2-3, 8-9 and 13-25 Under 35 U.S.C. 102(b) and In the Alternative Under 35 U.S.C. 103(a) Should Be Reversed

The Examiner has finally rejected Claims 1-4 and 7-10 stand are rejected under 35 U.S.C. 102(b) as being anticipated by, and in the alternative under 35 U.S.C. 103(a), as being obvious over, Lin et al., Chinese J of Biochemistry (Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao) (1999), 15(6), 974-977 ("Lin et al.").

This rejection should be reversed.

In making her rejection, the Examiner initially stated that Lin et al. discloses throughout the article, such as in the abstract that with the isocaudamers which have different recognition sequences and produce compatible cohesive ends, chimeric multi-epitope *Plasmodium falciparum* DNA vaccines including the multiplication of the single copy epitope and the tandem linkage of different kinds of epitopes were flexibly

[1] A search of the Office's full text database of patents issued since 1976 reveals that the term "predetermined appears in 1,312,500 issued U.S. patents.

constructed. The Examiner further stated that a specific B-cell response was detected by ELISA by Lin et al. after the immunization of BALB/c mice with the chimeric antigen, which demonstrated the usefulness of this strategy of constructing multi-epitope DNA vaccines. The Examiner concluded that the specific method steps of Lin using specific components fully meet the claimed method using broad components in the method.

The Examiner's conclusion of anticipation was not correct. Lin does not identically disclose applicants' presently claimed invention.

Anticipation under § 102 requires strict identity. "Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997). "Every element of the claimed invention must be literally present, arranged as in the claim." Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Lin does not disclose a number of the limitations of independent claims 13 and 22, and thus cannot anticipate the presently claimed invention.

While Lin discloses the use of isocaudamers having different recognition sequences to produce chimeric multi-epitope *Plasmodium falciparum* DNA vaccines, there is no disclosure of randomly assembling polyepitope chimeric genes with different lengths from the nucleic acid molecules encoding randomly combined bi-epitopes as is required by step (c) of each independent claim. Further, Lin does not disclose isolating polyepitope chimeric genes into a plurality of different length ranges, purifying and amplifying the isolated polyepitope chimeric genes, subcloning the purified and amplified polyepitope chimeric genes into expression vectors, or transforming prokaryotic hosts with the expression vectors to obtain polyepitope chimeric gene expression libraries, the expression libraries corresponding to different length ranges into which the polyepitope

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[2] A search of the Office's full text database of patents issued since 1976 reveals that the term "immunological type" appears in 54 issued U.S. patents, and "type" appears in 2,460,733 patents.

chimeric gene libraries were isolated. Further, Lin does not disclose assessing the diversity of the polyepitope chimeric genes in the expression libraries, and selecting at least one polyepitope chimeric gene library based on diversity for use in preparing chimeric gene vaccines. In addition, Lin does not disclose immunizing animals with the polyepitope gene expression libraries to provide expression products of the polyepitope chimeric genes. Nor does Lin disclose detecting the immunogenicity of the expression products of the polyepitope chimeric genes. Lin does not disclose selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope chimeric gene expression libraries and the immunogenicity of the expression products of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries. Finally, Lin does not disclose screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines.

In reply to applicants' arguments, the Examiner stated that the different argued lengths would have been inherently taught by Lin's description of the different recognition sequences (i.e., of different length) or would have been obvious to determine.

The Examiner further stated that the disclosure of Lin of the tandem linkage reads on the bi-epitopic claim. The Examiner further replied that since the polyepitope of Lin elicits antibody responses hence, the argued immunogenicity of the product would be inherent to the prior art teachings.

The Examiner referred to the PCT search report which cites this reference as an anticipatory reference.

The Examiner further stated that it would be within the ordinary skill in the art to isolate the different length ranges since as known in the art library produces a diverse (range) of compounds.

The Examiner states that this is recognized no less by applicants at e.g., paragraph [0038] which states ".....five groups of randomly assembled polyepitope chimeric genes of respectively 300, 800, 1200, 2000 and 4000 bp are separated. It is understood that one skilled in the art may set any desired length ranges."

However, because Lin does not expressly or inherently disclose at least one step of the presently claimed method, Lin cannot and does anticipate that invention. The Examiner's final rejection entered under 35 U.S.C. 102(b) over Lin et al. should be reversed.

Nor does Lin render the presently claimed invention obvious. There is no teaching, suggestion or motivation in Lin to, *inter alia*, randomly assemble the nucleic acids molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths, nor to isolate the polyepitope chimeric genes into a plurality of different length ranges, nor to clone the polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, nor to assess the diversity of those libraries. Thus, Lin would not render the presently claimed invention obvious to one or ordinary skill in the art at the time the invention was made.

The Examiner has failed to establish a *prima facie* case of obviousness, and the alternative rejection made under 35 U.S.C. 103(a) should be reversed.

E. The Rejection of Claims 2-3, 8-9 and 13-25 Under 35 U.S.C. 103(a) Over Sette et al. or Fikes et al. in view of Richards et al. or Applicants' Alleged Admission of Known Prior Art Should Be Reversed

Claims 2-3, 8-9 and 13-25 stand finally rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,026,443 ("Sette et al.") or U.S. Patent 6,602,510 ("Fikes et al.") in view U.S. Patent 6,291,214 ("Richards et al.") or applicants' admission of known prior art. This rejection should be reversed.

Sette et al. identifies and prepares human papilloma virus ("HPV") epitopes and epitope-based vaccines to HPV. The Examiner noted that Sette et al. disclose, among other things, a vaccine comprising a minigene that encodes a polyepitopic peptide, such as a minigene that encodes from 1 to 150 of the peptides identified by Sette et al. The Examiner further noted that Sette et al. provide guidance for creating and constructing polyepitopic compositions such as minigenes, such as selecting epitopes with sequences that meet predetermined criteria for conservancy, in Examples 10 and 11. The Examiner noted that Sette et al. disclose that a minigene expression plasmid typically contain supermotif or motif- bearing epitopes from multiple HPV antigens, preferably including both early stage and late stage antigens, so that multiple supermotifs and motifs are covered to ensure a broad population coverage. The Examiner also notes that Sette et al. disclosed in detail a method for constructing minigene-bearing expression plasmids.

The Examiner further noted that Fikes et al. disclose minigene vaccines encoding multiple epitopes, as well methods for creating a DNA sequence encoding selected epitopes for expression in human cells by reverse translating the selected epitopes, using a human codon usage table to guide the codon choice for each amino acid in the sequence, and then synthesizing corresponding oligonucleotide sequences encoding the plus and minus strands of the minigene which can be subsequently cloned into a desired expression vector. The Examiner also noted that Fikes et al. discloses two methods for functional testing of the minigenes, target cell sensitization, and immunogenicity.

The Examiner notes that Richards discloses the use of isocaudamers, namely Esp3A1 and Eco RI, to clone a cDNA into the pSK213 vector twice, once at the Eco RI site to include prokaryotic transcription and once at the Esp3A1 site to exclude transcription from occurring in *E. coli*.

The Examiner also noted that that the applicants state that isocaudamers are known in the art, and that they may be used in the practice of the present invention.

The Examiner concluded that it would have been obvious to one having ordinary skill in the art at the time the invention was made to use isocaudamer linkage in the method of either Sette or Fikes for the advantage taught by Richards above. The Examiner states that because of this known advantage, one would be motivated to use the isocaudamer linkage. The Examiner further states that one would have a reasonable expectation of success in obtaining a polyepitopic chimera gene vaccine since the isocaudamer linkage had been used, and is known in the art in making polyepitopic chimeric gene vaccine.

In response to the Examiner's rejection, applicants respectfully pointed out that the Examiner has not made out a *prima facie* case of obviousness of the presently claimed invention by the citation of these references.

There is nothing in any of the individual references, nor in any combination of the individual references, which would teach, suggest, or motivate one of ordinary skill in the art to employ the presently claimed method. In particular, there is no teaching or suggestion that isocaudamer linkages be employed to construct nucleic acid molecules encoding randomly combined bi-epitopes. Further, there is no teaching or suggestion that the nucleic acid molecules encoding bi-epitopes be randomly assembled into polyepitope chimeric genes with different lengths. Nor is there any teaching or suggestion that the resulting polymeric chimeric genes having different lengths be isolated into a plurality of different length ranges, purified, amplified and subcloned into expression vectors to obtain polyepitope chimeric gene expression libraries. Nor is there any teaching or suggestion that the diversity or immunogenicity of these expression libraries be assessed. Nor is there any disclosure or suggestion that the results of screening the expression libraries for diversity and immunogenicity be employed in

selecting at least one such expression library for further screening of clones from such expression libraries to identify individual polyepitope gene clones for use as vaccines.

Sette et al., who disclose polyepitope gene vaccines for HPV, actually teach away from the presently claimed invention by the method disclosed in their apparently prophetic Example 11 for constructing minigene multi-epitope DNA plasmids. Sette et al. disclose plasmids including multiple CTL and HTL peptide epitopes, such as HLA-A2 supermotif-bearing epitopes, HLA-A1 motif-bearing epitopes, HLA DR supermotif-bearing epitopes et al. Sette et al. advises including epitopes derived from multiple viral antigens, in order to ensure broad population coverage. However, Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene. Thus, one of ordinary skill in the art would, following the disclosure of Sette et al., construct polyepitope chimeric gene vaccines with no attempt to randomize the sequence of epitopes within the construct, and without any recognition that the sequence could have an effect on the immunogenicity of the construct.

Similarly, Fikes et al. discloses minigene vaccines incorporating multiple epitopes, but fails to disclose any recognition that the sequence of epitopes in the construct may have an effect on immunogenicity. Fikes et al. advises that optimized peptide expression and immunogenicity can be achieved by incorporating introns to facilitate efficient gene expression, and that expression can be increased mRNA stabilization sequences and sequences for replication in mammalian cells (co. 31, lines 35-42). However, Fikes et al. fail to disclose randomizing the sequence of epitopes in the construct and screening for optimized immunogenicity.

Thus, the combination of references cited by the Examiner does not make out a *prima facie* case of obviousness.

Following KSR Intern'l Co. vs. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d 1385 (2007), the Manual of Patent Examining Procedure at ¶ 2141 acknowledges that "[t]he

key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reasons why the claimed invention would have been obvious...." As summarized in this portion of the MPEP, various rationales (A-G) may support a conclusion of obviousness. However, none of the listed rationales are applicable to the present situation.

For example, a simple combination of the cited references does not yield the present invention, for the reasons listed above (rationale A). The invention cannot be categorized as a simple substitution of one element from another (rationale B) nor is it merely the use of known techniques to improve similar devices (methods, or products) (rationale C).

Further, the invention does not amount to applying a known technique to a known device (method, or product) ready for proving to yield predictable results (rationale D).

With respect to rationale E, an "obvious to try" standard, the invention cannot be categorized as simply choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

With respect to rationale F, there is no "known work in one field of endeavor" that "may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art".

Finally, with respect to rationale G, this follows the standard "TSM test", requiring some "teaching, suggestion or motivation in the prior art that would have led one of ordinary skill to modify the prior art references or to combine prior art reference teachings to arrive at the claimed invention". Again, since, as detailed above, it is submitted the references fail to disclose many aspects of the present invention, it is not seen how any theoretical combination of them could arrive at the present invention.

The Examiner replied to applicants' arguments stating that Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene are not commensurate in scope with the claims. The Examiner asserted that the claims do not recite any sequences.

The Examiner observed that applicants cannot attack the references individually when the rejection is based on the combination of references. The test for combining references is not what the individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art, citing In re McLaughlin, 170 USPQ 209 CCPA 1971. The Examiner observed that a court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art, citing In re Kuderna, 165 USPQ 575 CCPA 1970.

The Examiner concluded that while Sette et al. does not teach e.g., the isocaudamer linkage, as argued however, Richards does. The Examiner noted that Richards teaches the advantages in the use of isocaudamer, which is a well-known linkage, as admitted by applicants. The Examiner asserted that because the linkage method is well known in the art and because of its advantages one having ordinary skill in the art would be motivated to modify the method of Sette et al. or Fikes to arrive at the claim method.

Applicants respectfully note that the Examiner failed to respond to applicants' argument that the cited art did not disclose or suggest many if not most of the steps in the presently claimed method. In order to make out a *prima facie* case of obviousness, the Examiner has the burden of citing prior art which would teach or suggest each claim

limitation to one of ordinary skill in the art. As explained above the Examiner has not done so. This is legal error.

In reply to applicants' arguments, the Examiner objected that applicants' arguments that Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene are not commensurate in scope with the claims. The Examiner explained that the claims do not recite any sequences. However, applicants are not claiming any specific sequence, but rather a method for preparing a vaccine. Applicants' method includes steps that are not disclosed or suggested in any of the cited references, nor in any combination of them. Thus, the Examiner has failed to establish a factual basis for this rejection, and her legal conclusion of *prima facie* obviousness is in error and should be reversed.

The Examiner also comments that applicants cannot attack the references individually when the rejection is based on the combination of references; and that the test for combining references is not what the individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art, citing In re McLaughlin, 170 USPQ 209 (CCPA 1971). The Examiner further opines that a court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art, citing In re Kuderna, 165 USPQ 575 (CCPA 1970).

It is factual error for the Examiner to assert that the applicants have attacked the references individually. Applicants contend that there is nothing in the combination of references which would disclose, teach, or suggest a number of the method steps included in the instantly rejected claims to one of ordinary skill in the art. The Examiner has not identified anything in the cited art to the contrary.

The Examiner concludes that while Sette et al. does not teach e.g., the isocaudamer linkage, as argued however, Richards does. The Examiner notes that Richards teaches the advantages in the use of isocaudamer, which is a well-known linkage, as admitted by applicants. The Examiner concludes that because the linkage method is well known in the art and because of its advantages one having ordinary skill in the art would be motivated to modify the method of Sette et al. or Fikes to arrive at the claim method. This is legal error. The combination of Sette et al. or Fikes et al. with Richards or the allegedly admitted prior art would at most teach or suggest the first two of the eight steps of independent claim 13 and the five steps of independent claim 23. The Examiner has not even made a serious attempt to make a hindsight-guided reconstruction of the presently claimed invention. The rejection should be reversed.

VIII. Conclusion

Reversal of each of the rejections entered is respectfully requested.

Respectfully submitted,

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CLAIMS APPENDIX

CLAIMS ON APPEAL:

2. The method according to claim 13, wherein the randomly assembling of the polyepitope chimeric genes with different lengths in step c) is carried out simultaneously by following two methods: combined polymerase chain reaction and primer-free polymerase chain reaction, and isocaudamer linkage in the vector for random assembling.

3. The method according to claim 13, wherein the antigen of interest in step a) is an antigen related to infectious diseases, tumors or autoimmune diseases.

4. The method according to claim 3, wherein the antigen of interest in step a) is an antigen of *Plasmodium falciparum*.

8. The method according to claim 23, wherein the randomly assembling of the polyepitope chimeric genes with different lengths in step c) is carried out simultaneously by following two methods: combined polymerase chain reaction and primer-free polymerase chain reaction, and isocaudamer linkage in the vector for random assembling.

9. The method according to claim 23, wherein the antigen of interest in step a) is an antigen related to infectious diseases, tumors or autoimmune diseases.

10. The method according to claim 9, wherein the antigen of interest in step a) is an antigen of *Plasmodium falciparum*.

13. A method for preparing polyepitope chimeric gene vaccines, the method comprising the steps of:

a) selecting, synthesizing, and cloning into a vector a plurality of nucleic acid molecules each encoding a single epitope of an antigen of interest;

b) constructing nucleic acid molecules encoding randomly combined bi-epitopes in the vectors of step a) by isocaudamer linkage;

c) randomly assembling the nucleic acid molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths;

d) (i) isolating the polyepitope chimeric genes with different lengths into a plurality of different length ranges,

(ii) purifying and amplifying the isolated polyepitope chimeric genes,

(iii) subcloning the isolated polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries,

e) assessing the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries;

f) (i) immunizing animals with the polyepitope chimeric gene expression libraries to provide expression products of the genes;

(ii) detecting the immunogenicity of the expression products of the genes;

g) selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope gene expression libraries and the immunogenicity of the expression products of the genes in the polyepitope gene expression libraries; and

h) screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines.

14. A method according to claim 13 wherein the at least one polyepitope chimeric gene expression library is screened by at least one high-throughput immunochemistry method.

15. A method according to claim 13 wherein the expression libraries selected have high diversity as measured by single strand conformation polymorphism.

16. A method according to claim 13 wherein the expression libraries selected have polyepitope chimeric genes having a diversity of greater than 85%.

17. A method according to claim 13 wherein the expression products of the genes in the selected gene libraries have high immunogenicity.

18. A method according to claim 17 wherein the immunogenicity is determined in terms of antiserum titer.

19. A method according to claim 13 wherein the expression libraries selected have immunological characteristics related to a predetermined antigen epitope.

20. A method according to claim 19 wherein the predetermined antigen epitope relates to a specific immunological type.

21. A method according to claim 19 wherein the predetermined antigen epitope elicits the generation of a specific cytokine.

22. A method according to claim 19 wherein the predetermined antigen epitope elicits a cross-protective effect in an animal model.

23. A method for preparing polyepitope chimeric gene vaccines, comprising the steps of:

a) selecting, synthesizing and cloning into a vector a plurality of nucleic acid molecules each encoding a single epitope of an antigen of interest;

b) constructing nucleic acid molecules encoding randomly combined bi-epitopes in the vectors of step a) by isocaudamer linkage;

c) randomly assembling the nucleic acid molecules encoding by-epitopes of step b) into polyepitope chimeric genes with different lengths;

d) (i) isolating the polyepitope chimeric genes into a plurality of different length ranges,

(ii) cloning the polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, the expression libraries

corresponding to the different length ranges into which the polyepitope chimeric genes were isolated;

e) assessing the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries and selecting at least one polyepitope chimeric gene library based on diversity for use in preparing polyepitope chimeric gene vaccines.

24. The method of claim 23 further comprising (i) immunizing animals with the polyepitope chimeric gene expression libraries to provide expression products of the genes, and (ii) detecting the immunogenicity of the expression products of the genes;

25. The method of claim 23 further comprising screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use a polyepitope chimeric gene vaccines.

EVIDENCE APPENDIX

No previously submitted affidavit evidence is being relied upon by appellants.

RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a Court or the Board regarding any related appeals or interferences.